REMARKS

Reconsideration is requested.

Claims 1-15, 18, 19, 20, 37 and 43 have been canceled. Claims 16, 17, 21-36 and 38-42 are pending. Claims 27-35 have been withdrawn from consideration.

While pages 1 and 2 of the Office Action dated June 2, 2005 state that claims 27-35 have been withdrawn from consideration, the applicants note that the Examiner has also rejected (i.e., after examining) claim 27 under Section 112, first paragraph, on page 1. Clarification is requested as to whether claim 27 has been examined.

At a minimum, rejoinder and allowance of any withdrawn method claims to making and/or using an allowed product are requested.

A Decision on the Petition filed on July 14, 2004 (i.e., over a year ago) is requested. The Patent Office continued delay in rendering a Decision on the Petition filed July 14, 2004 is not understood and a Decision is requested prior to a further Action on the merits from the Examiner.

The Examiner's comment on page 2, paragraph 2 of the Office Action dated June 2, 2005 regarding the appropriateness of the prior final rejection of October 19, 2004 is not understood and clarification is requested. More importantly, MPEP § 706.07(e) suggests that the applicants request for withdrawal of a premature final rejection is to be considered by a Primary Examiner. As the Office Action of June 2, 2005 has not been signed by an Examiner other than Examiner Bao Q. Li, and there is no indication that Examiner Li is a Primary Examiner, reconsideration of the matter by a Primary Examiner, pursuant to MPEP § 706.07(e), is requested.

The specification has been amended above to include on page 85 the sequence identifiers from page 86 and the Sequence Listing. The amendment is believed to be completely responsive to the Notice to Comply dated June 2, 2005. The applicants also submit that neither a substitute paper nor computer readable copy of the "Sequence Listing", nor a Statement that their contents is the same, are required.

The Examiner is requested to hold in abeyance the obviousness-type double patenting rejections of claims 15, 16, 17, 18, 21-26, 36-39, 40 and 43 "over claims 13, 16 and 21 of U.S. Patent No. 6,635,257 B1 and the copending application No. 09/995,791", until such time as allowable subject matter is identified, at which time the applicants will consider filing a Terminal Disclaimer. The Examiner is requested to identify the claims of application Serial No. 09/995,791 which the Examiner believes are obvious variants of claims 15-18, 21-26, 36-39, 40 and 43 of the present application.

The Section 102 rejection of claims 16, 17, 20-26, 36-43 over Maertens (WO 96/04385A2) is traversed. Reconsideration and withdrawal of the rejection are requested in view of the following distinguishing comments.

As noted in the Amendment of February 22, 2005, the Section 102 rejection of claims 16, 17, 20-26 and 36-43 over WO 96/04385A2 is contrary to the Patent Office's position in the Office Actions dated July 2, 1999[1], February 24, 2000[2] and November

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[1] Examiner Zeman stated as follows in support of her assertion that the specification failed to show how to "make/or use" the invention:

"The above rejected claims are drawn to prophylactic peptide vaccine compositions. To be a prophylactic vaccine, the vaccine must provide protective immunity, demonstrable [sic] by viral challenge experiments, in a reasonable model system. The specification, as filed, does not set forth that the claimed composition provides any sort of protective immunity in any model system which can be extrapolated to humans or higher mammals. While the skill in the art of virology is high, to date, no vaccines for HCV have provided any protective immunity, so that the expectation of success in this endeavor is not high (Farci et al. 1997). Farci et al. states that HCV vaccines do not exist for HCV and would be highly unlikely to be efficacious, in view of the high reinfection rates. Given the lack of success

in the art, the lack of working examples, and the unpredictability of the generation of protective immunity the specification [sic], as filed, is not enabling for such vaccines.

[2] Examiner Zeman stated as follows in explaining why the specification failed to teach how to "make and/or use" the claimed invention:

"As set forth previously, the specification is devoid of working examples of demonstrating protection from viral challenge in a reasonable model system using any of the polypeptides of the invention. The area of protective vaccines, and the elicitation of protective immunity in HCV is highly unpredictable, as demonstrated by Farci (1992) and its contradictions with other art, such as the art cited by applicant.

Applicant submits Farci (1996) in support of his position. Farci (1996) vaccinated chimpanzees with polypeptides of E1. While some neutralizing antibodies were elicited to those peptides, escape mutants arose, and resulted in HCV infection of the animals. This is not the elicitation of a protective response, and is not a demonstration of an effective vaccine. Further, applicant has not indicated, or even suggested that the peptides of Farci (1996) are the same as, or similar to the peptides of the invention, nor is it clear that the peptides of Farci (1996) contain a T cell stimulating epitope, as required by the invention.

In regards to Choo et al (1994), Choo vaccinates the chimpanzees with full length E1/E2 complexes. The polypeptides of the invention are not all full length, not necessarily in complex with one another, and not necessarily from the same subtype as that of Choo et al. Determination of the elements required to match the results of Choo, using smaller peptides, remains unpredictable. And while Choo obtained protection in some animals, at least two animals became infected with HCV upon viral challenge. This is not evidence that the claimed polypeptides can provide protective immunity in response to challenge virus. Applicant's polypeptides are quite different from the immunogens used by Choo et al, such that one cannot automatically draw the same conclusions for Applicant's polypeptides. It is entirely unclear whether the individual polypeptides of the invention would function in the same manner as full length E1/E2 complexes.

Rosa (1996) discloses a test which estimates the levels of neutralizing antibodies to particular polypeptides of HCV. The presence of neutralizing antibodies is not a reliable indication of a protective immune response. Rosa uses full length E1, and a truncated E2 (aa384-715), which is still larger than the polypeptides of the invention. Rosa concludes that vaccination with certain proteins of HCV can correlate with the elicitation of neutralizing antibodies, and that *more than one epitope* on E2 is required for these effects. Again, as the polypeptides of Rosa are significantly different than the polypeptides of the invention, one cannot automatically draw the same conclusions. It is not clear that the polypeptides of the invention possess both epitopes identified by Rosa as being important for the generation of neutralizing antibodies. Even if the peptides of the invention did possess those epitopes, there is no evidence that those neutralizing antibodies are protective in an *in vivo* situation.

Applicant has submitted two abstracts by the inventors, describing vaccine experiments using purified E1 protein. These experiments appear to have used full length E1 protein, and not the shorter polypeptides of the invention, thus the conclusions of Maertens cannot immediately be applied to the polypeptides of the invention. Further, the polypeptides of the invention are not limited to those purified by a particular method, or limited to any particular subtype of HCV such that no direct comparisons or conclusions can be made.

Diepolder (1997) submitted by Applicant, identifies a immunodominant polypeptide with T cell stimulating epitopes, however this epitope is not within E1 or E2, and Diepolder does not investigate vaccination and challenge experiments with that polypeptide. The relevance of Diepolder to the claimed invention (therapeutic vaccines) is unclear.

Finally, Botarelli (1993) investigates the T cell stimulating ability of 6 recombinant HCV proteins. Botarelli uses full length E1 and E2 proteins, and is unable to draw solid conclusions as to their T cell stimulating ability in the patients sampled. No conclusions as to protection from further infection are set forth by Botarelli.

Given the lack of success in the art, the lack of a correlation between the art and the invention, the lack of working examples in the specification, and the unpredictability of the generation of protective immunity, the specification, as filed, is not enabling for such vaccines."

15, 2000[3] in Serial No. 08/928,757. While the present Examiner notes that "each application is treated on its own merits" (see, page 4 of the Office Action dated June 2, 2005), the Examiner is also requested to see MPEP § 706.04 which includes the following instruction:

> "Full faith and credit should be given to the search and action of a previous examiner unless there is a clear error in

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[3] Examiner Zeman stated as follows in support of her assertion that the specification of Serial No. 08/928,757 failed to teach one of ordinary skill to make and/or use the claimed invention:

"As set forth previously, the specification is devoid of working examples demonstrating protection from viral challenge in a reasonable model system using the polypeptides of the invention. The area of protective vaccines, and the elicitation of protective immunity in HCV is highly unpredictable, as demonstrated by Farci (1997) and its contradictions with other art, such as the art cited by the applicant.

Applicant submits Farci (1996) in support of his position. Farci (1996) vaccinated chimpanzees with polypeptides of E1. While some neutralizing antibodies were elicited to those peptides, escape mutants arose, and resulted in HCV infection of the animals. Further, applicant has not indicated, or even suggested that the peptides of Farci (1996) are the same as, or similar to the peptides of the invention, nor is it clear that the peptides of Farci (1996) contain a T cell stimulating epitope, as required by the invention.

In regards to Choo et al (1994), Choo vaccinates the chimpanzees with full length E1/E2 complexes. The polypeptides of the invention are not full length, and determination of the elements required to match the results of Choo, using smaller peptides, is not predictable. And while Choo obtained protection in some animals, at least two animals became infected with HCV upon viral challenge. Applicant's polypeptides are quite different from the immunogens used by Choo et al, such that one cannot automatically draw the same conclusions for applicant's polypeptides. It is entirely unclear whether the polypeptides of the invention would function in the same manner as full length E1/E2 complexes.

Rosa (1996) discloses a test which estimates the levels of neutralizing antibodies to particular polypeptides of HCV. Rosa uses full length E1, and a truncated E2 (aa384-715), which is still lager than the polypeptides of the invention. Rosa concludes that vaccination with certain proteins of HCV can correlate with the elicitation of neutralizing antibodies, that more than one epitope on E2 is required for these effects. Again, as the polypeptides of Rosa are significantly different than the polypeptides of the invention, one cannot automatically draw the same conclusions. It is not clear that the polypeptides of the invention possess both epitopes identified by Rosa as being important for the generation of neutralizing antibodies.

Applicant has submitted two abstracts by the inventors, describing vaccine experiments using purified E1 protein. These experiments appear to have used full length E1 protein, and not the shorter polypeptides of the invention, thus the conclusions of Maertens cannot immediately be applied to the polypeptides of the invention.

Diepolder (1997) submitted by applicant, identifies a immunodominant polypeptide with T cell stimulating epitopes, however this epitope is not within E1 or E2, and Diepolder does not investigate vaccination and challenge experiments with that polypeptide.

Finally, Botarelli (1993) investigates the T cell stimulating ability of 6 recombinant HCV proteins. Botarelli uses full length E1 and E2 proteins, and is unable to draw solid conclusions as to their T cell stimulating ability in the patients sampled.

Given the lack of success in the art, the lack of a correlation between the art and the invention, the lack of working examples in the specification, and the unpredictability of generation of protective immunity, the specification, as filed, is not enabling for such vaccines."

> the previous action or knowledge of other prior art. In general, an examiner should not take an entirely new approach or attempt to reorient the point of view of a previous examiner, or make a new search in the mere hope of finding something."

As for the Examiner's quote from Robert L. Harmon in the sentence spanning pages 4-5 of the Office Action dated June 2, 2005, the Examiner is requested to provide a complete copy of the relevant section of the reference so that the undersigned may review the complete passage as well as any case law which forms the basis of the quoted conclusion. The Examiner's reliance on Mr. Harmon's conclusion appears to be based on a confusion by the Examiner with case law that indicates that an anticipatory reference need not teach a utility of the alleged anticipatory product. Such case law does not however state that such a reference also need not teach how to at least make and/or use the alleged anticipatory product.

The quoted conclusion of Mr. Harmon, to the extent it can be understood to be applied by the Examiner in the present context, is contrary to the following opinion of Judge Bryson:

> "To anticipate a claim, a reference must disclose each and every element of the challenged claim and enable one skilled in the art to make the anticipating subject matter." See, PPG Industries Inc. v. Guardian Industries, Corp., 37 USPQ 2d 1618, 1625 (Fed. Cir. 1996) (emphasis added).

The quoted conclusion of Mr. Harmon, to the extent it can be understood to be applied by the Examiner in the present context, is contrary to the following opinion of Judge Newman:

> "To serve as an anticipating reference, the reference must enable that which is asserted to anticipate. "A claimed invention cannot be anticipated by a prior art reference if the

> allegedly anticipatory disclosures cited as prior art are not enabled." Amgen, Inc. v. Hoechst Manion Roussel, Inc.,.... 65 USPQ 2d 1385, 1416 (Fed. Cir. 2003). See, Bristol-Myers Squibb v. Ben Venue Laboratories, Inc., ...58 USPQ 2d 1508, 1512 (Fed. Cir. 2001) ("To anticipate the reference must also enable one of skill in the art to make and use the claimed invention."); PPG Industries, Inc. v. Guardian Industries Corp.,.....37 USPQ 2d 1618, 1624 (Fed. Cir. 1996) [quoted above]". See, Elan Pharmaceuticals Inc. v. Mayo Foundation for Medical Education and Research, 68 USPQ 2d 1373, 1375-1376 (Fed. Cir. 2003).

Copies of the above-quoted PPG and Elan opinions of the court are attached for the Examiner's consideration. Given the Patent Office's previous assertions regarding the alleged insufficiencies of the disclosure of Serial No. 08/928,757, it is submitted to be inappropriate to now assert the contrary opinion that the disclosure of Serial No. 08/928,757, as the published document WO 96/04385A2, teaches how to make and/or use a vaccine of the presently claimed invention. Withdrawal of the Section 102 rejection of claims 16, 17, 20-26 and 36-43 over WO 96/04385A2 is requested.

Beyond the above, the Examiner will appreciate from a review of, for example, Example 12 of the present application that, WO 99/67285 provides the starting materials of the currently claimed therapeutic vaccine composition, WO 99/67285 is the origin of U.S. Patent No. 6,635,257, which is the parent of the current application. As WO 99/67285 was required, with additional steps, to make the claimed composition, the same could not have been completely available from the cited WO 96/04385. The Examiner's double patenting rejection of the present claims over U.S. Patent No. 6,635,257 supports the applicants position that the present claims, like the claims of U.S. Patent No. 6,635,257, are patentable over WO 96/04385. Withdrawal of the

Section 102 rejection of claims 16, 17, 20-26 and 36-43 over WO 96/04385, is requested.

The Examiner further asserts the following as a basis for the Section 102 rejection over WO 96/043850A2:

> WO 96/043850A2 conveys possession of the composition by disclosing its full structure and a method of making the same." See, page 5 of the Office Action dated June 2, 2005.

This conclusion of the present Examiner is completely contrary to the above-quoted passages of Examiner Zeman's assessment of the exact same disclosure six years ago. The Patent Office may be able to treat each application "on its own merits" however the Patent Office should not be allowed to deny the applicants' assignee benefit of their early disclosure of Serial No. 08/928,757, when prosecuting the application, and then grant the Patent Office and the public the benefit of that same disclosure in asserting that it is enabling prior art when the applicants' assignee provides further evidence which was earlier asserted to be required for enablement.

Finally, with regard to the Section 102 rejection of the claims over WO 96/043850A2, the Examiner asserts that the recitation of a "therapeutic vaccine" lends no patentable weight. This also is contrary to the Patent Office's prior positions where claims to "compositions" were allowed where claims to "vaccines" are regularly rejected for an alleged lack of enablement.

Withdrawal of the Section 102 rejection of the claims over WO 96/043850A2 is requested.

The specification has been amended at page 75, line 9, to refer to WO 99/67285, to obviate the objection of the disclosure noted on page 6, paragraph 14, of the Office Action dated June 2, 2005. Withdrawal of the objection is requested.

The objection to the specification stated on page 6, paragraph 15, of the Office Action dated June 2, 2005, is traversed. Support for the noted phrase "specific oligomeric envelope E1 protein" may be found, for example, at page 6, lines 5-8 of the specification. Support for the noted phrase "a part thereof" may be found, for example, at page 2, lines 28-30; page 16, lines 21-22; page 25, line 34 to page 26, line 11; and page 36, lines 28-30 of the specification. Withdrawal of the objection to the specification is requested.

The Section 112, second paragraph, rejection of claims 16, 17, 21-26 and 36-43 stated in paragraphs 17 and 18 on page 6 of the Office Action dated June 2, 2005 is traversed. Reconsideration and withdrawal of the rejection are requested in view of the disclosure of, for example, page 6, lines 5-8 of the specification.

Claims 37 and 43 have been canceled, without prejudice, to obviate the Rule 75 objections stated in paragraphs 19-22 of the Office Action dated June 2, 2005. Withdrawal of the objections are requested.

The Examiner is requested to hold in abeyance the provisional obviousness-type double patenting rejections stated in paragraphs 27-33 of the Office Action dated June 2, 2005 until allowable subject matter is identified, at which time the applicants will consider whether filing a Terminal Disclaimer would be appropriate.

The Section 112, first paragraph, rejection of claims 16-17, 20-27 and 36-43 is obviated by the above amendments. Withdrawal of the Section 112, first paragraph rejection is requested.

The claims are submitted to be in condition for allowance and a Notice to that effect is requested.

The Examiner is requested to correct the record by forwarding a revised PTO-892 listing the previously-cited "Lechner" document as being published in "Philos Trans R Soc Lond B Biol Sci 2000 Aug. 29; 355 (1400):1085-92" as would be found in electronic and other databases by one of ordinary skill in the art.

Respectfully submitted,

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